Some experience with biomarker driven cancer clinical trials

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SWOG

Outline

- Statistical Considerations (prior talks)
  - Impact of treatment and biomarker(s) on patient outcome (predictive and prognostic associations)
  - Impact of design choices on inference
- Experience
  - S9704 Prognostic Targeting
  - S1406 Single mutation (or subgroup) targeting
  - S1400 Multiple sub-group targeting

Traditional divisions of treatments by types of cancer

- Sites: Breast, Lung, Gastrointestinal, Genitourinary, Melanoma, Leukemia, Lymphoma, Myeloma, Sarcoma
- Traditional trials in sub-sites, histologies, early stage, advanced stages relapsed disease
- But increasingly disease is characterized molecularly into much finer divisions

Variation in efficacy

- Genetic or protein measurement (designing statistical interactions)
  - HER2 amplification [Herceptin]
  - EGFR mutation [Erlotinib]
  - tyrosine kinase enzyme (c-kit) [Imatinib]
  - BRAF mutation [Vemurafenib]
- Multi-variable genetics predicting treatment efficacy
  - OncotypeDx recurrence score (breast cancer)
  - Other Tumor genomics

Stages of treatment testing(learning)

- Phase I
  - The safe dose range, side effects, early activity.
- Phase II
  - Sufficient promise for further testing, more side effect assessment, refinement of dose, evidence of disease subtypes with most promise and feasibility.

Modeling

  - Some design examples: single arm 2-stage, single arm pilot, multi-arm randomized (screening or selection).
- Phase III
  - Formal comparison of new treatment to “standard”.

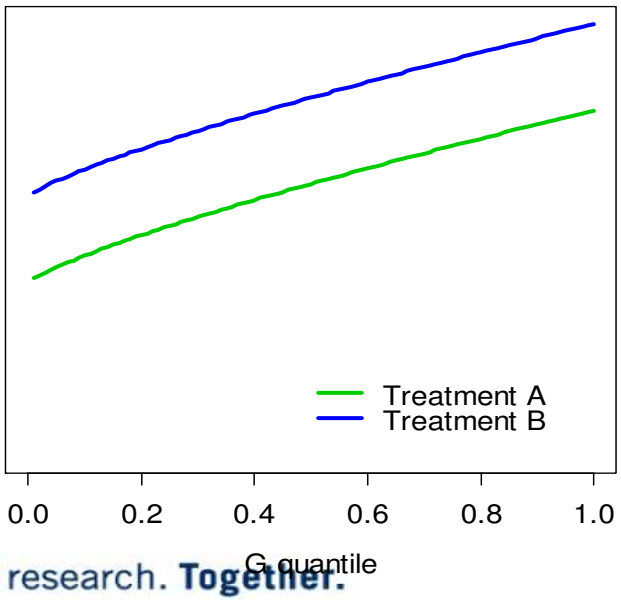
Modeling

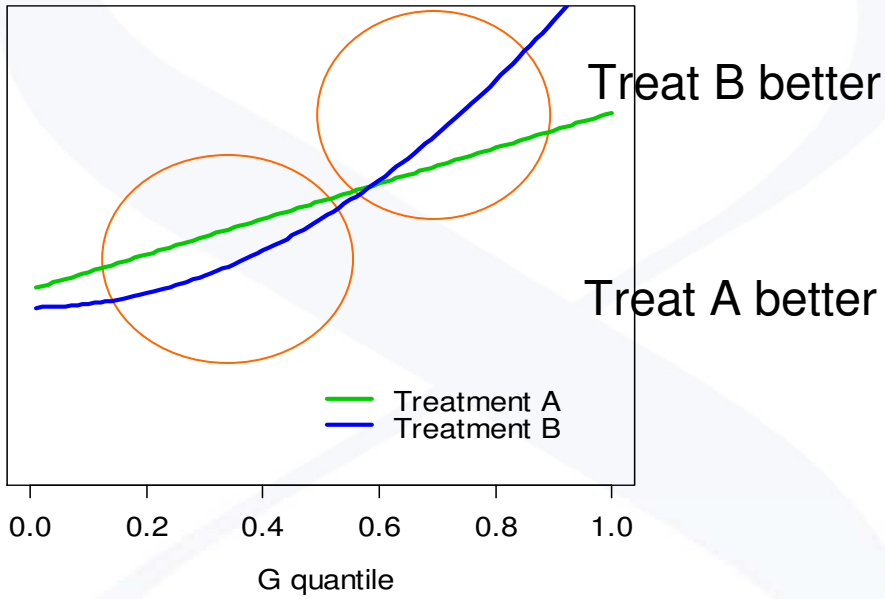
Outcome Associations in Trials: Choosing Target Design

- Biomarker - Treatment Interaction Model

  Two cases:

  - 1) Treatment is essentially equally effective regardless of gene
  - 2) The expression indicates where one treatment is preferred





General Case: Discrete Subgroup Models

For designing treatment trials, summaries based on a subgroup of patients are often useful.

At least 3 components are of interest:

1. Rules to describe a subgroup of patients, R.
2. A model for treatment effect in that group
3. The mass (or the fraction of all patients in that group)

$$R = \{X \geq c\}$$
$$M(R) = \theta(Z|X \in R)$$

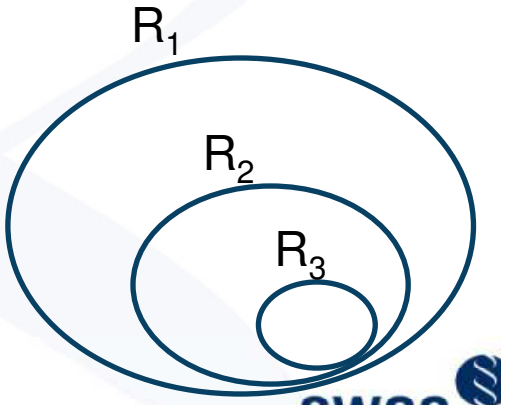
Eligibility $\longrightarrow$ $(R, M(R), \nu(R))$ $\longleftarrow$ Fraction of patients

- The triple describes future design properties
- Example of subgroup models

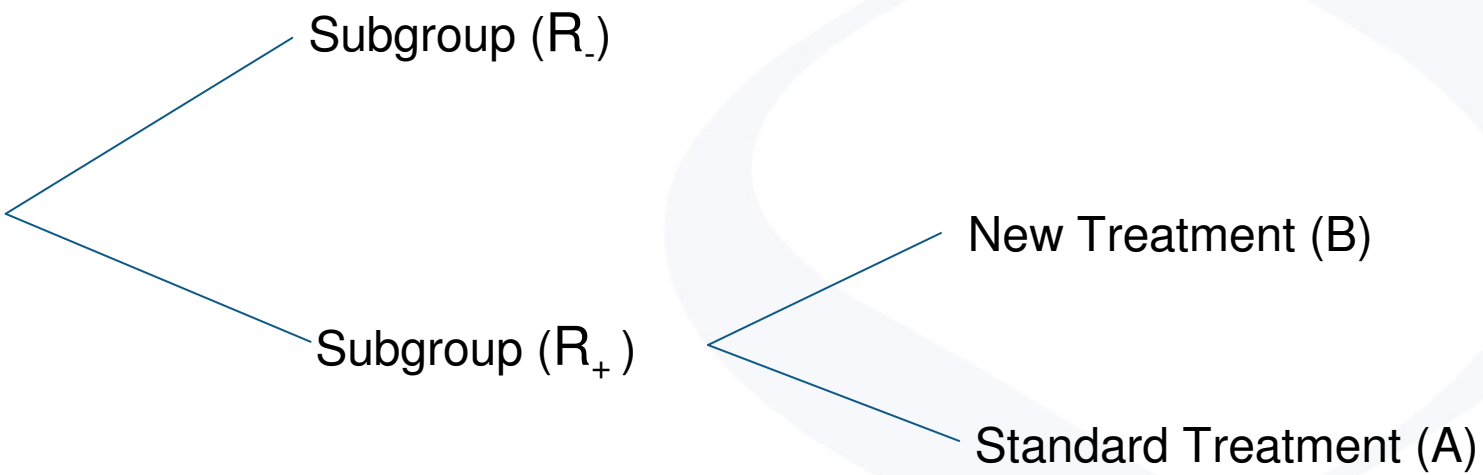
$$M(R) = \theta(Z|X \in R) = \alpha(R) + \beta(R)Z$$

Main effect

Treatment effect



Model Class 1: Targeted Design

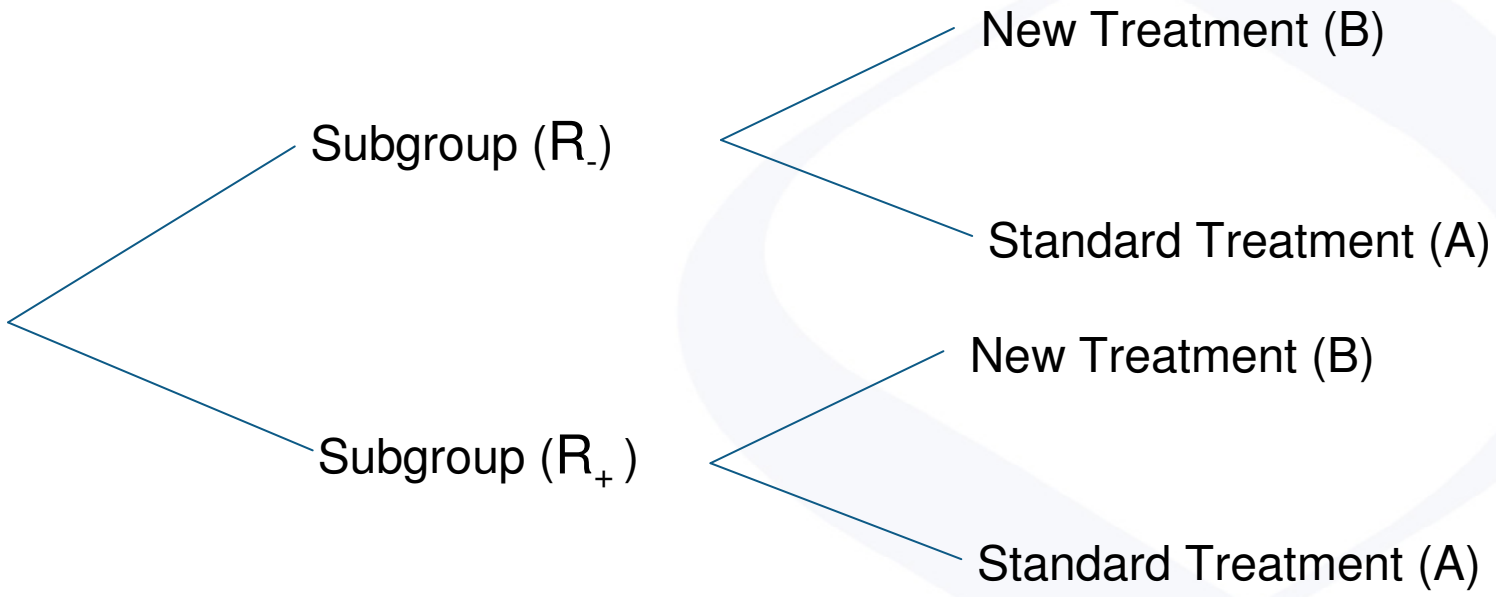


Advantages: If treatment is only effective in a subgroup this is powerful. However, if there is broader activity or if the goal is to assess a marker, then this is not a good design.

Model Class 2: Stratified Design

Options: Stratification overall test, subgroup+overall testing, interactior tests

Measure prospectively or retrospectively



This is not a good design if one believes treatment can only be efficacious for (R_+) group.

SWOG: a diverse network and part of US NCTN

- Network of 650+ sites, including:
  - 40 core member institutions
  - ~14 strongly associated Lead Academic Participating Sites
  - 28 NCI-designated cancer centers
  - 27 Community Clinical Oncology Programs
  - 27 SPORES
  - Extensive collaboration within Canada
  - Sites in Europe, Middle East, Latin America, Asia
- Membership includes:
  - More than 5,000 researchers & clinicians
  - Almost 5,000 research nurses & clinical research associates

The Past: A design based on a prognostic model: SWOG 9704

S9432 Phase II pilot study: High Dose Therapy with Transplant for Newly Diagnosed KI67 Positive Diffuse Aggressive Lymphoma

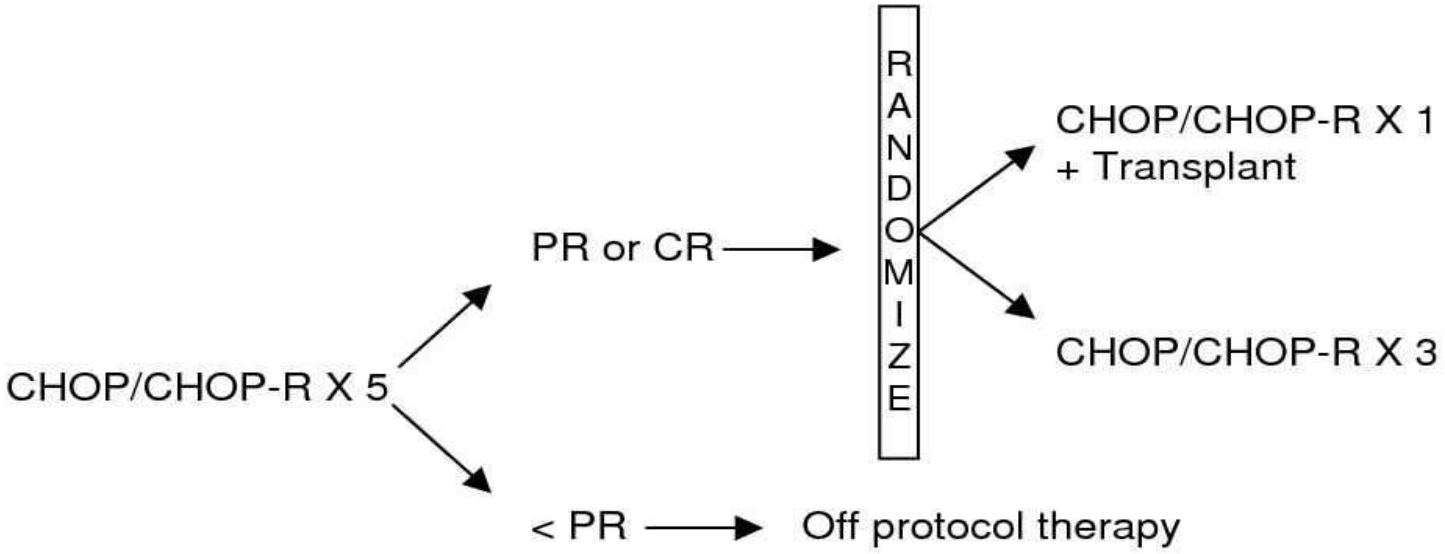
- Based on KI67 proliferation model from prior samples
- Identified a very poor risk group
- KI67>80% cell staining
  - 3 year OS of 18% versus 56% . This population is appropriate for high dose chemotherapy and transplant [optimistic difference]
  - 18% of patients with diffuse aggressive lymphoma have a KI67 > 80% [small subgroup size]
- Frozen tissue/paraffin was sent to University of Arizona
- “Real” time communication back to institution to determine treatment assignment
- Study closed due to poor accrual (3 patients)

Alternative prognostic model and supportive data

- International prognostic index (IPI) for lymphoma developed from a large data base
- Combination of multiple easily measured clinical variables; no need for tissue
- IPI=Stage II vs. III/IV, low vs. high LDH, performance status 0-1 vs. ≥ 2, > 1 extra nodal site
  - High-Int risk ≥ 3 factors, High Risk ≥ 4 factors
- Retrospective analysis of a French Phase III study supporting high dose therapy in poor prognostic group, the high-intermediate risk which was approximately 30% of the patients

S9704: A Randomized Phase III Trial Comparing Early High Dose Therapy and Autologous Stem Cell Transplant to Conventional Dose CHOP/R Chemotherapy for Patients with Diffuse Aggressive Non-Hodgkin's Lymphoma in High-Intermediate and High Risk Groups

ymphoma
rognostic Index >=3
-ligh-Int + High Risk)

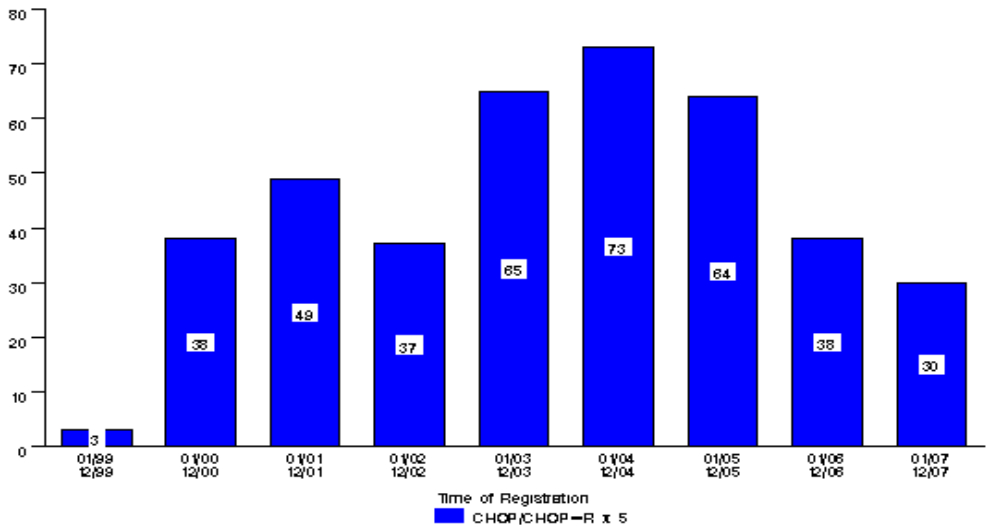


370 Eligible

253 Eligible for randomization

S9704 Timeline

- S9704 Activated 9/15/97
- Results from a large randomized study CHOP vs. CHOP-Rituximab showing improved survival for CHOP-R.
- Rituximab was added for all B-cell CD20+ lymphomas on 4/1/03
- Chose not to redesign the trial to target only B-cell CD20+ patients
- Trial closed 12/17/07 after reaching its randomization accrual goal



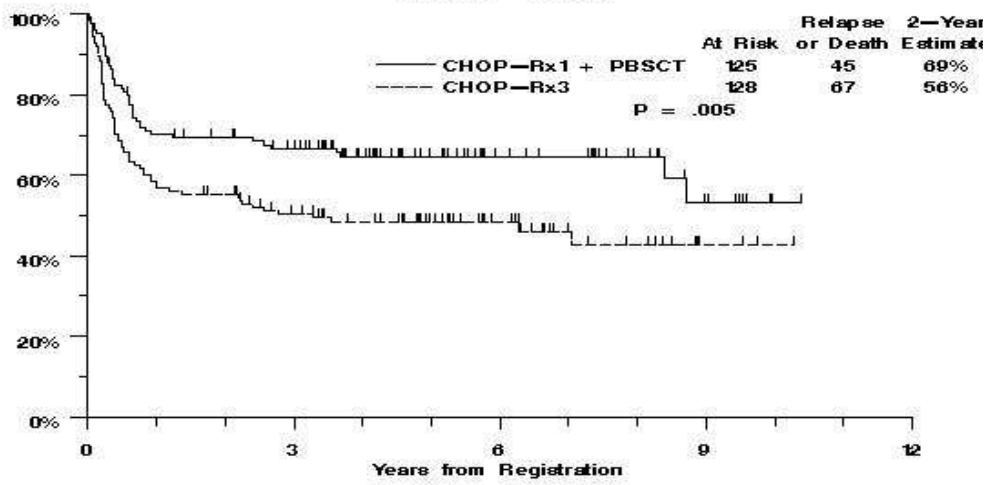
S9704 Results: Grade III–IV Toxicities

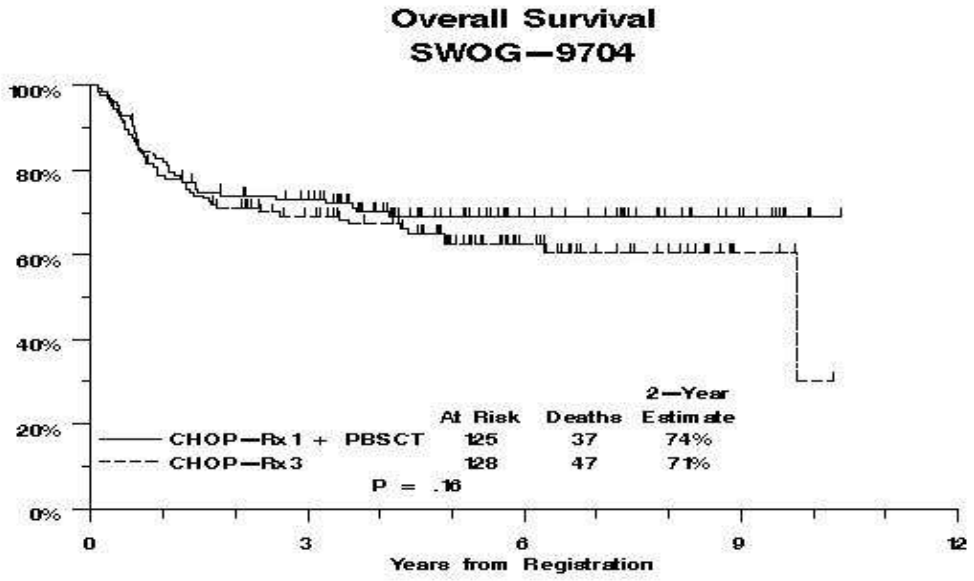
Toxicities	CHOP (R) x 1 + ASCT (%)	CHOP (R) x 3 (%)
Infection	**50**	**13**
GI	**26**	**5**
Metabolic	**13**	**1**
Lung	**11**	**2**
CV	**10**	**4**
Neurologic	**7**	**2**
Hypoxia	**4**	**0**
Hepatic	**3**	**0**
Treatment deaths	**6**	**2**

N=253 randomized patients

Outcome of randomized patients

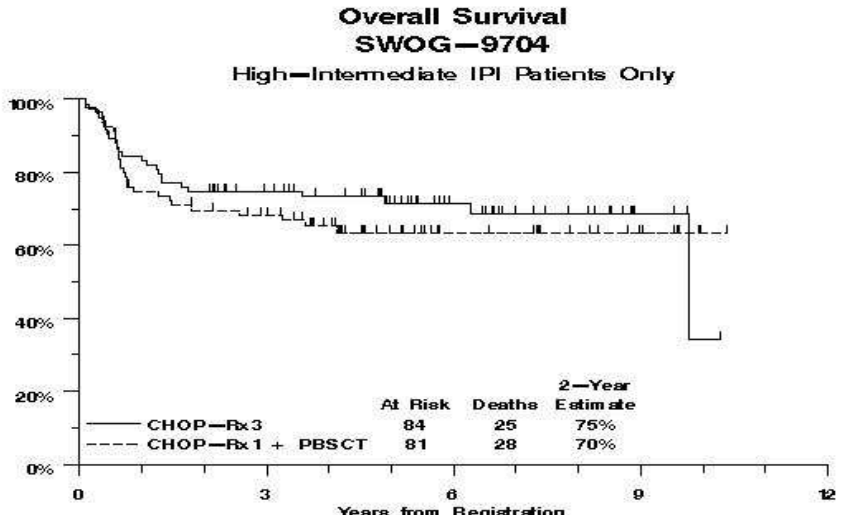
- Targeting the poor prognostic subgroup identified a group that benefited for PFS but not OS
- Some suggestion of greater effect in the highest risk group (interaction p-value . 02).

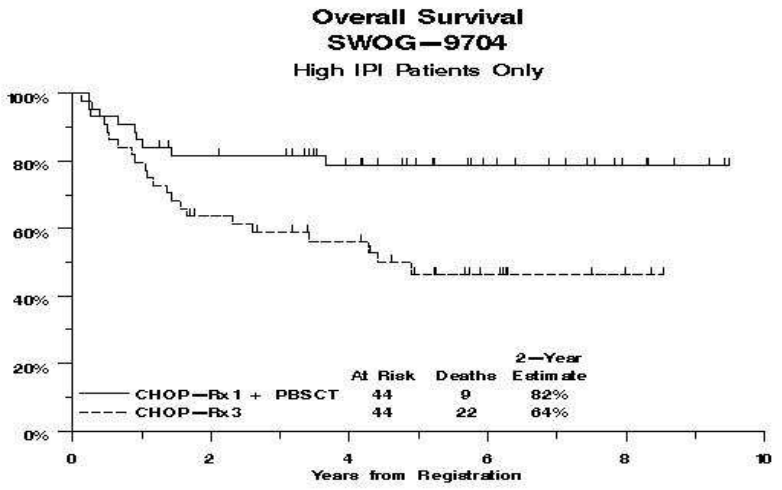




S9704 Highest Risk IPI Subgroup

- While only exploratory there was suggestion of an effect in the highest risk group
- Was the poor prognostic group targeting not sufficiently aggressive?

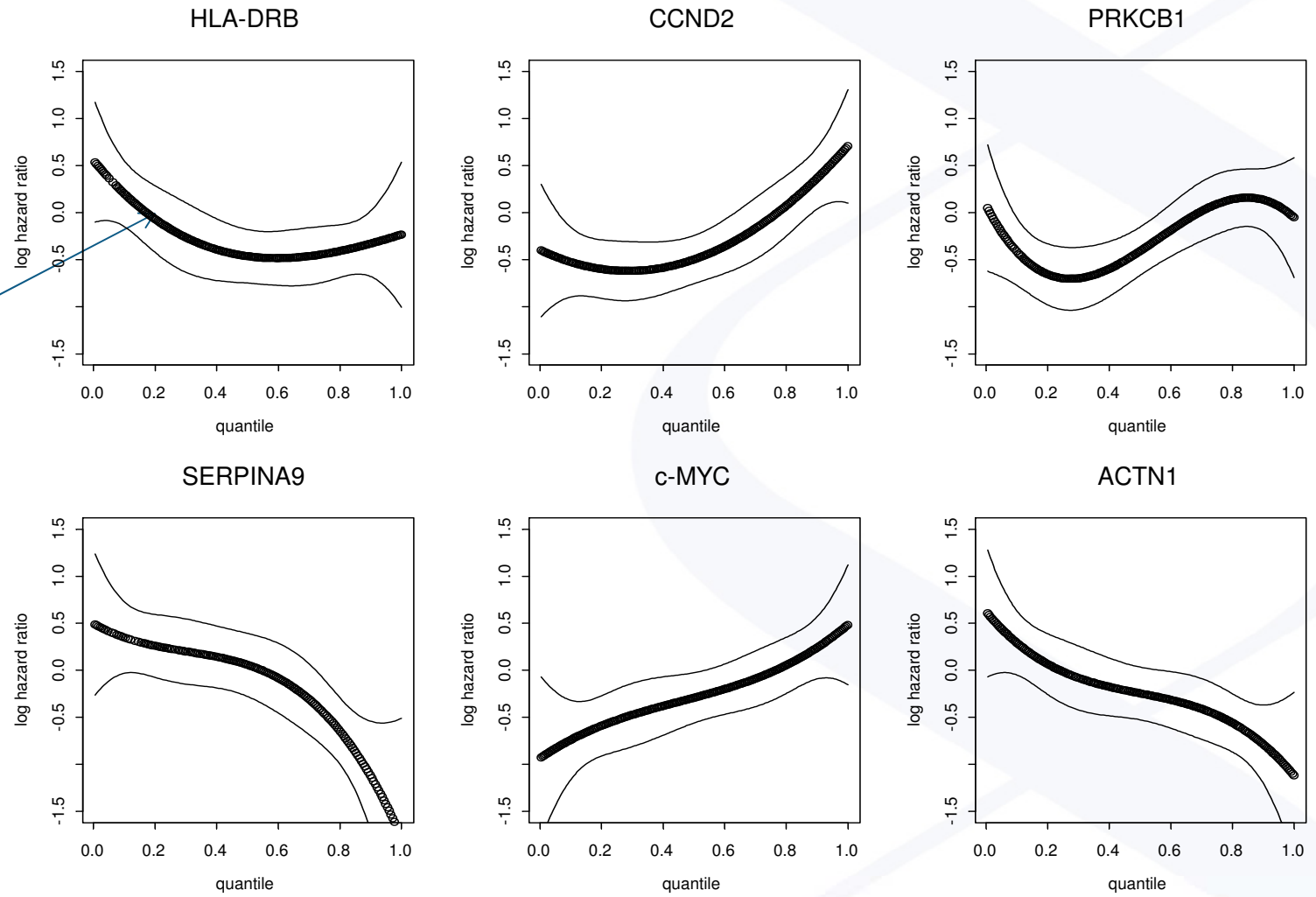




Diffuse Large Cell Lymphoma: Gene Expression on archived tissue specimens (same disease as S9704)

- Gene expression arrays (quantitative, large numbers)
  - Fresh or frozen tissue (problematic for multi-institutional studies, also often a problem wrt to use of historical samples)
- Gene expression from paraffin (array plate technology) <100 genes
  - Great for our multi-institutional cooperative group studies
- Data from several clinical trials.
  - Both before and after the introduction of Rituxan therapy to standard chemotherapy
- Analysis focused on overall prognostic effect, no evidence of interactions

Hazard rates for multiple genes for DLBCL



ubgroup?

Rimsza et al. 2011

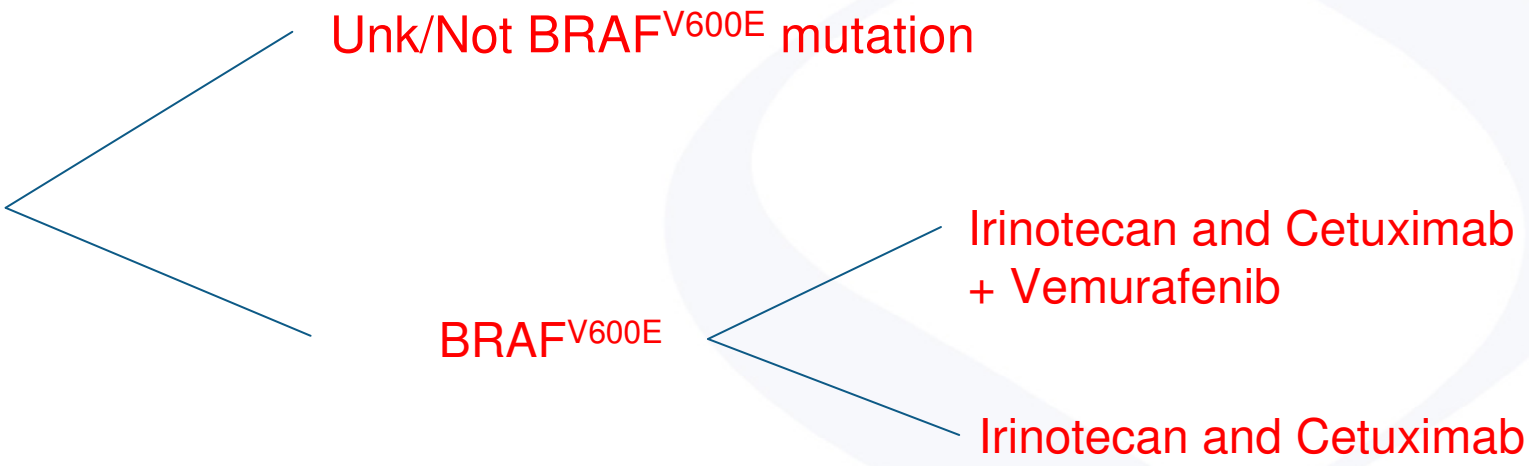
Practical Issues

- The biomarker wasn't workable yet in S9432.
- The fraction of high risk patients (targeted group was less than expected.
- There were questions of when to hold the design fixed and when to be more flexible. It was a practical choice for S9704 not to redesign mid-trial after the introduction of Rituximab for the B-Cell subgroup.
- Given the limited sample sizes available, we need to consider modeling based on data from multiple sources to guide targeting.

Recent Past and Present

- Recently multiple examples of genomic or other biomarker targeted studies
- Antje Hoering presented SWOG studies
  - Lung Cancer Study S0819
  - Breast Cancer Study S1007
- Many more – but with some general themes
  - Typically a single target group
  - Many issues with respect defining target

S1406 Randomized Phase II study of Irinotecan and Cetuximab with or without Vemurafenib in BRAF Mutant Metastatic Colorectal Cancer



Example of targeting (on mutation at time): If treatment is only effective in a subgroup this is powerful

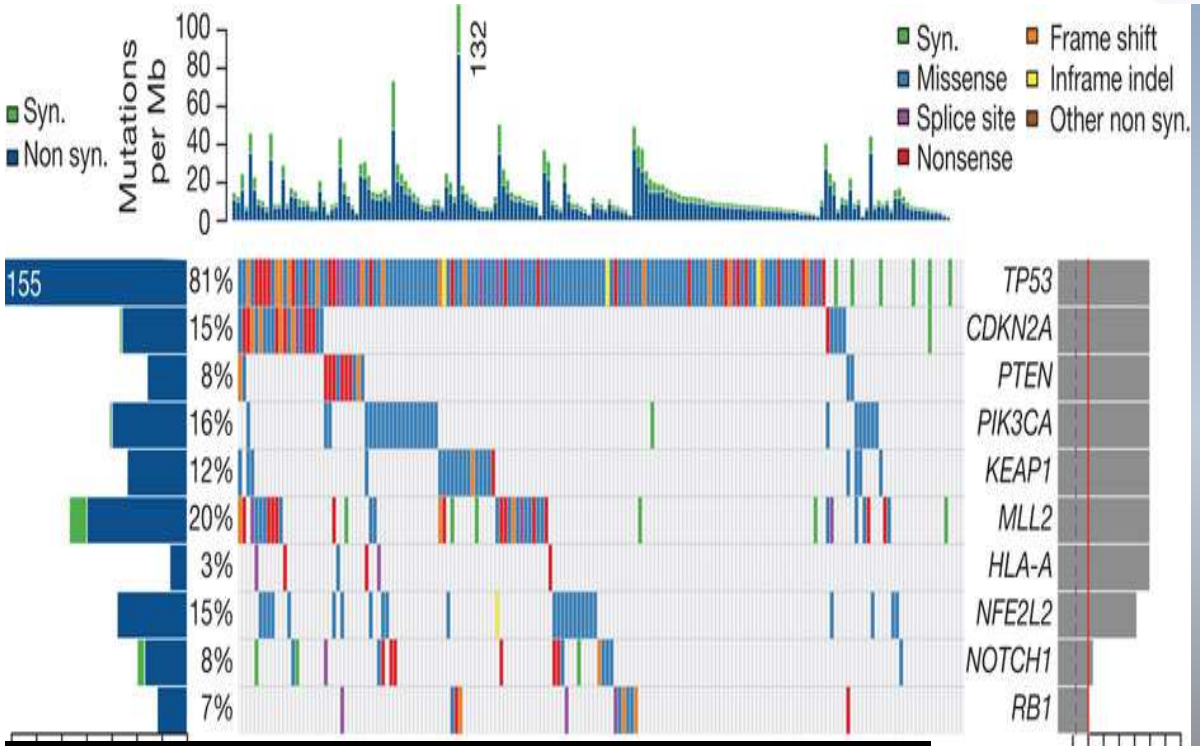
Special: Embedded Patient-Derived Xenograft Co-Clinical Trial

A New Present: Lung-Map S1400

- Special thanks to Mary Redman (slides and more)

Also in Canada in Q1 or Q2 of 2015 (hopefully) !

Unmet needs addressed by a Master Protocol

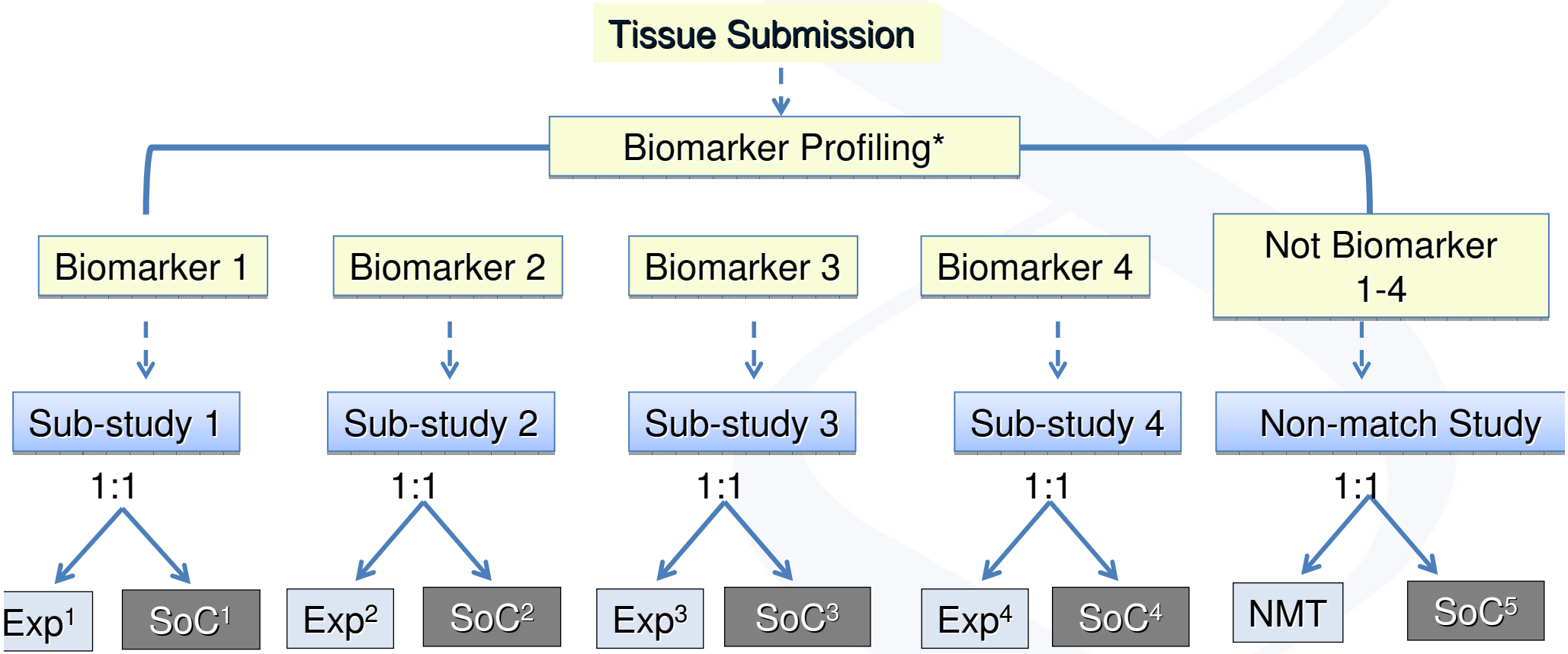


Significantly mutated genes in lung SQCC

PS Hammerman *et al. Nature* **000**, 1-7 (2012)
doi:10.1038/nature11404

- **How to develop drugs for uncommon-rare genotypes?**
- **How to apply broad-based screening (NGS)?**
- **How to achieve acceptable turn-around times for molecular testing for therapy initiation? (<2 weeks)**
- **How to expedite the new drug-biomarker FDA approval process? (companion diagnostic)**

Master Protocol Design



Sub-studies assigned based on biomarker results, patients with multiple biomarkers randomly assigned to sub
udy.
xp = Targeted therapy (TT) or TT combinations (TTC), Exp^{1-4} are different TT/TTC regimens
MT = non-match study experimental therapy or combinations
oC = docetaxel or erlotinib, SoC^{1-5} depends on biomarker and TT/TTC/NMT regimen

Study Design and Objectives

Design:

Independently conducted and analyzed parallel Phase II/III studies

Primary Objectives within each sub-study:

Phase II Component:

1. To evaluate if there is sufficient evidence to continue to the Phase III component by comparing progression-free survival (PFS) between patients randomized to experimental therapy versus SoC.

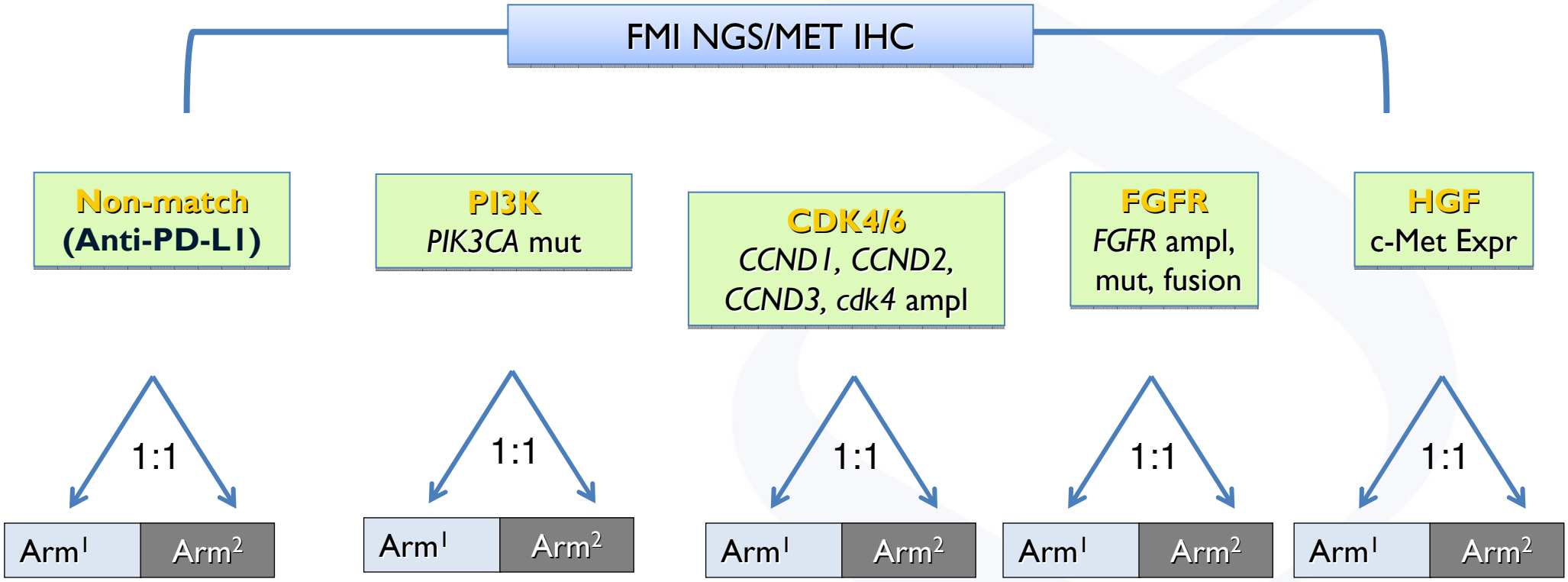
Phase III Component:

1. To determine if there is both a statistically and clinically-meaningful difference in PFS between the treatment arms.
2. To compare overall survival (OS) between treatment arms.

Goals

- Improve screening
  - Screening large numbers of patients for multiple targets
  - Reduce screen failure rate
  - Provide a sufficient “hit rate” to engage patients & physicians
- Increase speed of drug evaluation and development:
  - Provide an infrastructure to open new sub-studies faster
  - Rapid drug/biomarker testing for detection of “large effects”
  - Facilitate FDA approval of new drugs and bring safe & effective drugs to patients faster

Lung-MAP current sub-studies



[1] Medi4736
[2] Docetaxel

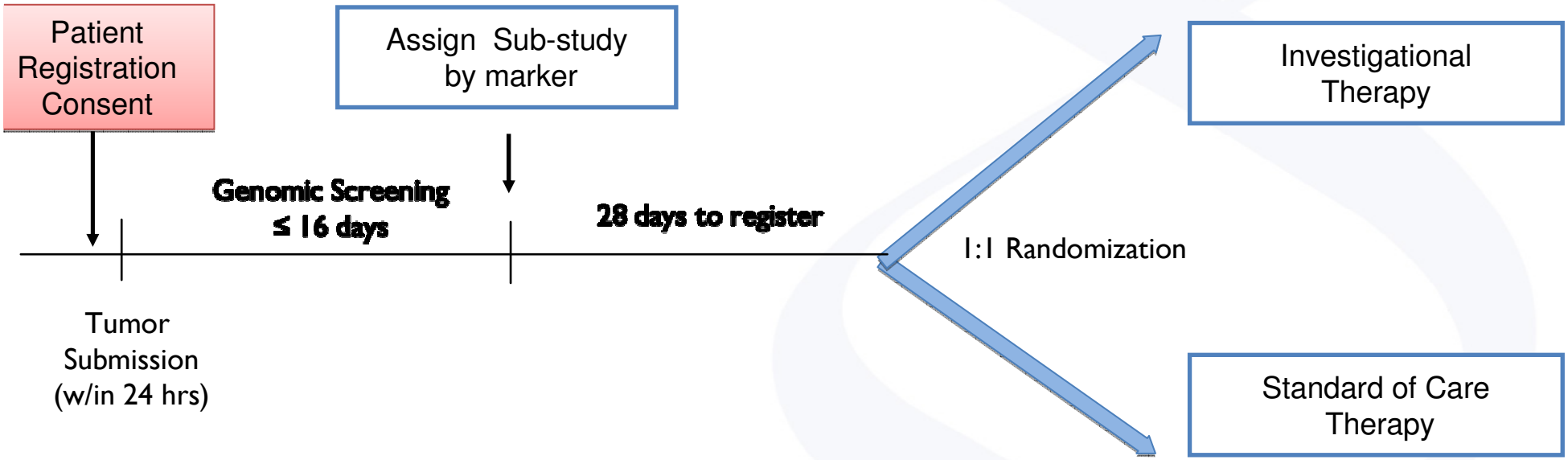
[1] GDC-0032
[2] Docetaxel

[1] Palbociclib
[2] Docetaxel

[1] AZD4547
[2] Docetaxel

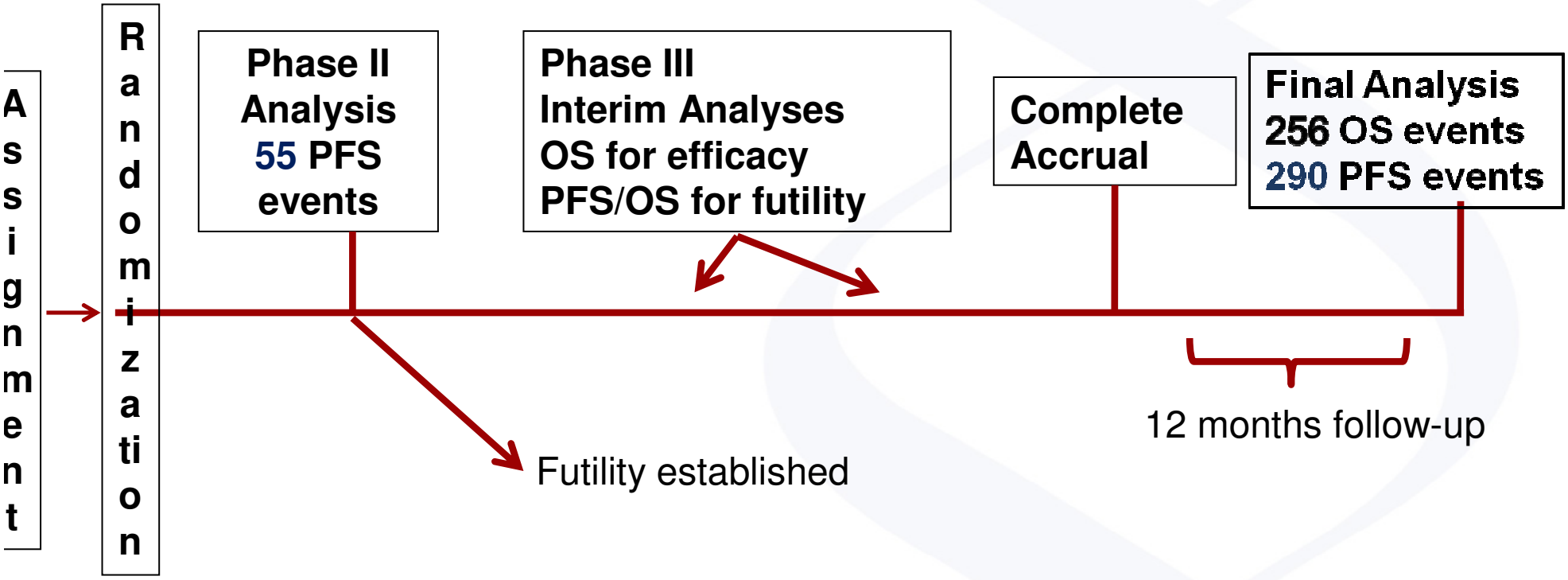
[1] Rilotumumab
+ erlotinib
[2] Erlotinib

Patient-Sample Schema



Central genomic screening:
Foundation Medicine: NGS test platform
Clarient: c-MET IHC

Study Design Within Each Sub-study



Statistical Design: Phase II Interim Analysis

	Phase II Design	
	Plan A	**Plan B**
Primary Outcome	**PFS**	
Sample Size	**55 progression events**	
Target HR (% improvement)	**HR = 0.5 2-fold increase**	**HR=0.4 2.5-fold increase**
Power	**90%**	**95%**
Type I error	**10%**	**4%**
Approx. Threshold to continue:		
HR % improvement	**HR= 0.71 41% increase**	**HR = 0.61 63% increase**

Each sub-study can choose between Plan A or Plan B to determine “bar” for continuation past Phase 2 interim analysis

Statistical Design: Phase III

	PFS and OS Co-primary	
	PFS	**OS**
Events	**290**	**256**
Null Hypothesis (HR)	**0.75* (33% improvement)**	**1.0 (equivalence)**
Alternative Hypothesis	**0.5 (2-fold increase)**	**0.67 (50% improvement)**
Type I error (1-sided)	**0.014 against HR = 1.33 < 0.00001 against HR = 1**	**0.025**
Power	**90%**	**90%**

** Non HR = 1 null hypothesis encodes clinical significance*

Sample size based on OS for all studies

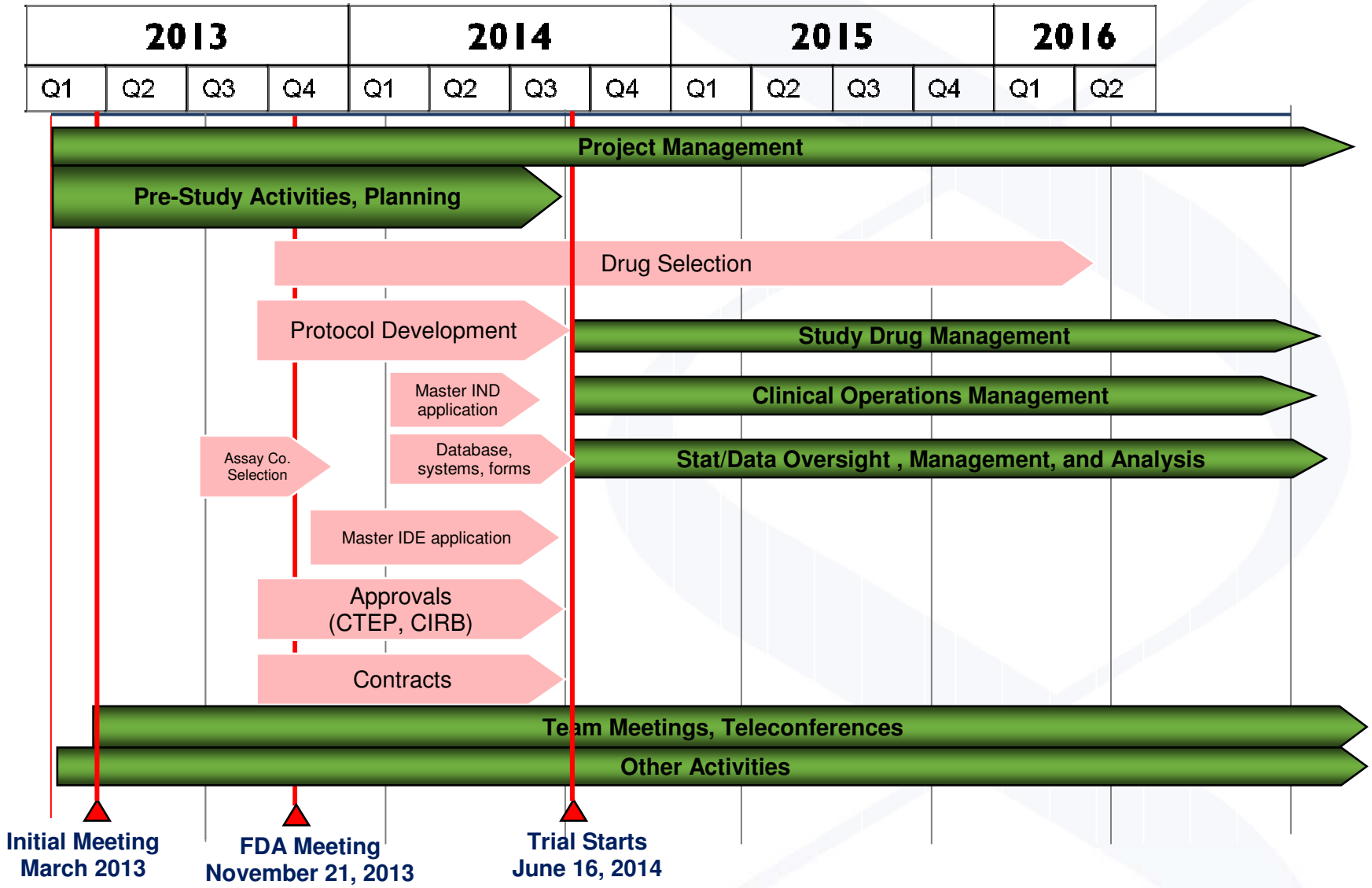
Sample Size for the Sub-studies

		Phase 2		Phase 3	
ub-study ID	Prevalence Estimate[1]	Approximate Sample Size	Approximate time of analysis	Sample Size	Approximate time of analysis
400A(non-match)[2]	56%	170	8	400	21
400B(PI3K)[3]					
GNE+	6%	78		288	
FMI+	8%	152	19	400	72
400C(CDK4/6)	12%	124	11	312	45
400D (FGFR)	9%	112	11	302	53
400E (HGF)	16%	144	9	326	37

Prevalence estimates: 35% with 1; 8% with 2; 0.8% with 3; 0% with 4 biomarkers
S1400A design and minimum PD-L1+: 50 (phase 2), 114 (phase 3) patients
S1400B design: eligibility based on FMI criteria, but designed around subgroup defined to be GNE+ (assumed ~70% of FMI+)

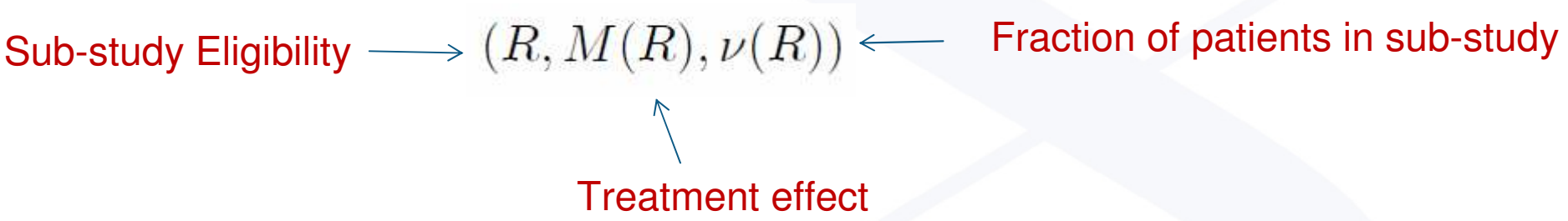
LUNG-MAP

Study development time-line



Design Issues

- Master study - but how much variation by sub-study for design specifications?
- Different target efficacy by sub-study
- Additional assay(s) added to FMI assay
- Frequency of marker subgroups – what sub-study frequency remains feasible?



Complex study lessons learned

- Communicate early and often with partners
  - OPEN(registration) saw Lung-MAP as one study, but we were planning to activate it as six.
  - Better specifications for how the marker data would be received. Plan for change (Central IRB , new assays)
  - Improved communication with pharmaceutical partners and institutions regarding SWOG structure, attributes and processes

Learning more from Master protocols

- Impact of dynamic multiple sub-study design and inference (as genotype groups open and close patient population changes)
- Opportunities for modeling of treatment effects are possible based on detailed genomic data and additional use of specimens

$$(R, M(R), \nu(R))$$

Acknowledgments

Collaborators

- Key statistical center Lung-MAP team:
  Lead Statistician: Mary Redman
- Design methods: Antje Hoering, John Crowley
- Target subgroup modeling: Charles Kooperberg

End